EBioMedicine 12 (2016) 22–23

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Clinical Islet Xenotransplantation: A Step Forward

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ARTICLE INFO

Article history:
Received 21 September 2016
Accepted 21 September 2016
Available online 24 September 2016

With the encouraging results of pancreatic islet allotransplantation, increasing attention is being directed towards pig islet xenotransplantation, which would resolve the problem of islet supply (Markmann et al., 2016; Ekser et al., 2012). Free (nonencapsulated) pig islets (either wild-type or genetically-engineered) have maintained normoglycemia in immunosuppressed diabetic nonhuman primates for >1 year (Park et al., 2015). Immunoisolated (encapsulated) pig islets have maintained normoglycemia in non-immunosuppressed diabetic nonhuman primates for up to 6 months (Dufrane et al., 2006).

Groth et al. performed the first clinical islet xenotransplantation in 1994 using fetal porcine islet-like cell clusters placed under the kidney capsule (Groth et al., 1994). Although clinical benefit was not demonstrated, evidence was provided by measurement of porcine C-peptide that porcine islets could survive in the human body. The first nationally-regulated clinical trial of intra-peritoneal alginate-poly-L-ornithine-alginate (APA) encapsulated (neonatal) porcine islet xenotransplantation in nonimmunosuppressed diabetic patients was carried out in New Zealand and was associated with some reduction in hypoglycemic unawareness (Matsumoto et al., 2014). However, there was a lack of correlation between the number of islets transplanted and the clinical outcome; the transplantation of 5000 IEq/kg was associated with better results than of 15,000 or 20,000 IEq/kg.

In this issue of *EBioMedicine*, Matsumoto et al. report the second clinical trial of nationally-regulated encapsulated porcine islet xenotransplantation, conducted in Argentina (Matsumoto et al., 2016). From their previous experience, the authors speculated that a large islet mass was susceptible to injury from oxygen and/or nutrient insufficiency, resulting in cell death. To avoid this problem, the islets were transplanted in two steps, with the second transplant being carried out 3 months after the first. In order to transplant a total of 10,000 IEq/kg or 20,000 IEq/kg, patients received either 5000 IEq/kg $\times$ 2 ($n = 4$) or 10,000 IEq/kg $\times$ 2 ($n = 4$) of encapsulated neonatal porcine islets in their peritoneal cavity by laparoscopy.

Although the study demonstrated significant improvement in HbA1c and reduction of hypoglycemic unawareness events with an improved transplant estimated function (TEF) score for up to 2 years post-transplant, the reduction of insulin dose was marginal or none. (Importantly, there was no evidence of complications from the transfer of porcine endogenous retroviruses.)

Although this second carefully-supervised trial is a step forward in the field of clinical islet xenotransplantation, several aspects need consideration before large-scale clinical trials will become justified (van der Windt et al., 2012).

(i) The number of islets obtained from the source pigs
Neonatal pigs may have some advantages as sources of islets (discussed by Nagaraju et al., 2015), one of which is their potential to proliferate after transplantation (which is not believed to be the case with adult islets). Whether there was any evidence that this occurred in the present study was not reported. However, it is reasonable to anticipate that 'neonatal' pigs (newborn to 5 days old) may provide a yield of up to 25,000 islets, and 'young' pigs (7–22 days old) may provide up to 30,000 islets. A 70 kg patient would therefore require 700,000 islets (70 $\times$ 10,000 IE/kg) or, more likely, 1.4 million islets (70 $\times$ 20,000 IE/kg), indicating that a single patient would require islets from approximately 25–50 piglets. With 8–12 piglets in each litter, this would be feasible. If, however, there is confirmed evidence of proliferation of the islets after transplantation, the number of piglets required may be fewer.

(ii) Encapsulation of pig islets and the immune response
Although the great theoretical advantage of the transplantation of encapsulated islets is that exogenous immunosuppressive therapy may not be required, the long-term viability of the encapsulated islets remains questionable. The dilemma in APA-based encapsulated islets is that, if the islets are not revascularized, they are likely to become exhausted (and die) from lack of nutrients and oxygen, particularly as some fibrin accumulates around the capsules, possibly reducing their permeability. In contrast, if the islets are revascularized, they are likely to become susceptible to injury from an immune or inflammatory response. There is already evidence that APA-based microencapsulated porcine islets induce an inflammatory response, upregulating inflammatory

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.08.034.
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http://dx.doi.org/10.1016/j.ebiom.2016.09.023

> cytokines and activating innate immune cells, such as tumor necrosis factor-α, IL-6, interferon-γ, macrophages, neutrophils, and dendritic cells (Cooper et al., 2016). The great deficiency of the present study is that the authors did not investigate whether there was an immune response to the islets (or capsules), though they speculated that microcapsules might shed xeno-antigens which activate the recruitment of CD^{4+}T cells and macrophages around the capsule. It will be essential to determine whether there is an immune response to the pig islets. If there is, either modification of the capsules or the administration of exogenous immunosuppressive therapy will be necessary, unless the islets can be completely protected by genetic manipulation of the pig.

Our own opinion is that it will be difficult to totally protect the encapsulated islets from the effects of cytokines and chemokines and possibly other components of the immune response, and therefore some immunosuppressive therapy may prove inevitable, thus negating the major theoretical advantage of 'immunoisolation'. Nevertheless, as the number of pancreases from deceased humans that become available will never suffice to cure all patients with T1D, the pioneering studies by Matsumoto and his colleagues are important and timely.

Disclosure

The authors declared no conflicts of interest.

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